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Gender-Based Mortality Follow-Up from the Program on the Surgical Control of the Hyperlipidemias (POSCH) and Meta-Analysis of Lipid Intervention Trials

Women in POSCH and Other Lipid Trials

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Objective
The authors assessed the clinical results of lipid-lowering therapy in women.

Summary Background Data
The Program on the Surgical Control of the Hyperlipidemias (POSCH) has demonstrated that effective lowering of total cholesterol and low-density lipoprotein cholesterol in a postmyocardial infarction population significantly reduces atherosclerotic coronary heart disease (ACHD) mortality, ACHD mortality combined with a new confirmed nonfatal myocardial infarction, and the number of coronary artery bypass grafting and angioplasty procedures performed.

Methods
A review and meta-analysis were performed of the seven primary or secondary lipid/atherosclerosis intervention trials—including POSCH—published in the English-language literature that included women and published results in women separate from the results in men or in the entire trial population. The main outcome measure analyzed was overall mortality.

Results
The Scottish Physicians Clofibrate Study, the Newcastle upon Tyne Clofibrate Study, and the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I) Trial may have demonstrated a possible benefit in ACHD prognosis from effective lipid intervention in women. The other four available trials did not. The Minnesota Coronary Survey reported a 15.6% increase in overall mortality rate and a 30.6% increase in a combined cardiovascular endpoint rate in the lipid-intervention group. The Upjohn Colestipol Study demonstrated statistically significant

reductions in overall and ACHD mortality in the men, but not in the women. The Scandinavian Simvastatin Survival Study (4S) showed highly statistically significant reductions in overall and ACHD mortality in the total trial population, but not in the 827 women in this study. For the 78 women in POSCH, there was no evidence of clinical benefit in the lipid-intervention group. Subjecting these seven studies to meta-analysis for overall mortality, a statistically significant reduction in this clinical endpoint was observed in the men, but not in the women. Assuming independent binomial distributions, the probability of obtaining statistical significance, with a two-sided alpha of 0.05, in a study of 7066 women (the combined number of women in the seven trials) would be >0.90 against an alternative of the magnitude observed in men.

Conclusions

These observations have at least two possible interpretations: either the mechanism of coronary obstruction is different in men than in women, or the mortality rate in the women in the reviewed studies is too low for a statistically significant result. Nonetheless, the available clinical trial data fail to demonstrate any overall mortality or other convincing clinical benefits from effective lipid intervention in women.

The Program on the Surgical Control of the Hyperlipidemias (POSCH) is a secondary lipid/atherosclerosis intervention trial. It demonstrates the following: effective lowering of total cholesterol levels by 22.6% and low-density lipoprotein (LDL) cholesterol levels by 36.3%, with an increase in the high-density lipoprotein (HDL) cholesterol levels by 5.7%, is associated with a statistically significant reduction in atherosclerotic coronary heart disease (ACHD) mortality, in the combined endpoint of ACHD mortality and confirmed nonfatal myocardial infarction, and in a >60% lowering in the number of coronary artery bypass grafting and angioplasty procedures performed. During the formal tenure of POSCH ending on July 19, 1990, statistically significant reductions in overall mortality and in ACHD mortality were not observed.[1] Follow-up for an additional 5 years subsequently has demonstrated a statistically significant reduction in ACHD mortality. To evaluate mortality endpoints further, to follow the long-term outcome of partial ileal bypass surgery (the intervention modality employed in POSCH), and to document the long-term results of effective lipid lowering in POSCH subgroups, including women, POSCH has been continued to at least 1998.

The results in the POSCH women were reported first in 1992 at the 112th Annual Meeting of the American Surgical Association.[2] Their lipid response and sequential coronary arteriographic findings were comparable to those observed in the POSCH men.[1,3,4] A statistically significant reduction in arteriographic disease progression was seen in the women and the men in the partial ileal bypass intervention group. At that time, overall mortality and ACHD mortality were slightly higher in women in the intervention group than in the control group. However, the women in the surgery subgroup had a 31.0% reduction in the combined endpoint of ACHD mortality and confirmed nonfatal myocardial infarction, and the women in the POSCH group with an ejection fraction ≥ 50% had a 22.6% reduction in overall mortality. None of these clinical effects in the women were statistically significant. We concluded in 1992 that the lipid modification in the women in the POSCH group reduced their atherosclerosis progression, and that these findings supported an aggressive treatment strategy for hyperlipidemia in women. We presumed that other lipid/atherosclerosis intervention trials that included women would provide evidence confirming this assumption.

In an ongoing assessment of the POSCH data, however, it was surprising to find that, unlike the male patients in POSCH, the female patients did not demonstrate comparable clinical benefits from lipid intervention over time. This finding stimulated this review of the published reports of lipid/atherosclerosis intervention trials that included women and provided results in the women apart from the men or from the total study population. The overall mortality results are subjected to meta-analysis.

METHODS

Selection of Studies

To qualify for inclusion in this review, the lipid/atherosclerosis intervention trial must have included women and must have published data that could be encoded to allow separate analysis of the women with re-

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spect to clinical endpoints. Many trials, therefore, were not suitable for evaluation because they were confined to men (*e.g.*, St. Thomas' Atherosclerosis Regression Study,[5] Coronary Drug Project,[6] Cholesterol Lowering Atherosclerosis Study,[7] Familial Atherosclerosis Treatment Study[8]) or did not present the results in women independently from the total study population (*e.g.*, British Corn Oil Study,[9] National Heart, Lung, and Blood Institute Type II Coronary Intervention Study,[10] Multicentre Anti-Atheroma Study[11]). There have not been any lipid/atherosclerosis intervention trials designed to assess clinical or arteriographic endpoints exclusively in women.

Statistical Analyses

In addition to a narrative and tabular presentation of the results in women from each trial, the data have been subjected to meta-analysis by two different methods—the fixed effects model, using risk ratios determined by the classical Mantel-Haenszel method,[12] and the DerSimonian and Laird random effects model,[13] with the results reported as risk ratios and risk differences. The fixed effects model assumes a common treatment effect across the studies being pooled, with differences primarily due to sampling variations. Studies are weighted by the inverse of the within study variances. The random effects model incorporates between-studies variations in addition to within-study variations. In practice, when heterogeneity of treatment effect is present, the random effects model tends to be more conservative and gives a wider confidence interval. In the absence of heterogeneity, both statistical models give the same answer. Because a linear regression of the treatment rate on the control rate showed the two to be correlated, the meta-analytic results are presented in the descending order of the control rate.

We elected to submit overall mortality to meta-analysis because each of the seven analyzable studies provided overall mortality data. Because only four of the studies reported ACHD mortality results, a meta-analysis of ACHD mortality was not performed. Because meta-analysis of heterogeneous combined cardiovascular endpoints could be suspect, we chose not to subject the combined endpoint findings provided in five of the trials to meta-analysis.

Possible inequalities in the distribution by random assignment to control and intervention groups in the POSCH women based on 14 baseline variables were tested by individual Student's t tests[14] and by Cox regression analysis,[15] and the current POSCH life-table analysis was assessed using the Mantel-Haenszel statistic.[16] All results are analyzed by two-sided tests for significance; a p value ≤ 0.05 was considered to be statistically significant.

RESULTS

Trial Summaries and Results

Scottish Physicians Clofibrate Study

The Scottish Physicians Clofibrate Study[17] employed one of the first fibric acid drugs (clofibrate) as the intervention modality. It was a secondary intervention study because the inclusion criteria required evidence of preexisting ACHD. However, the inclusion criteria were quite protean and the design of the analysis was unusually complex, making it difficult to interpret the reported 6-year outcomes. The overall mortality rate for men was 10.5% (32/305) in the placebo group and 11.5% (33/288) in the clofibrate group. For the women, the overall mortality rate was 9.7% (6/62) in the placebo group and 1.6% (1/62) in the clofibrate group (Table 1). A first nonfatal myocardial infarction (both definite and probable) occurred in 35 of 305 men (11.5%) in the placebo group and in 22 of 288 men (7.6%) in the clofibrate group. For the women, the corresponding numbers were 6 of 62 (9.7%) in the placebo group and 3 of 62 (4.8%) in the clofibrate group (Table 1). The reduction in the total cholesterol between the last two annual measurements in the women (70 mg/dL) was twice that seen in the men (35 mg/dL). The changes in triglycerides were not reported.

Newcastle upon Tyne Clofibrate Study

The Newcastle upon Tyne Clofibrate Trial[18] demonstrated a possible benefit in ACHD prognosis from effective lipid intervention in women. Comparable to the Scottish Physicians Clofibrate Study, this trial also used clofibrate, a drug with a powerful triglyceride-lowering effect, as the intervention modality. However, neither study published the precise triglyceride effect observed. Against a corn oil placebo, the total cholesterol reduction at 6 months in the Newcastle upon Tyne Clofibrate Trial favored the women: 41 mg/dL in the women *versus* 28 mg/dL in the men. These reductions were maintained throughout the 5 years of the study.

According to the authors, the beneficial clinical findings were not predictable from the magnitude of the cholesterol or triglyceride reductions. The majority of the results of this study were presented as incidence rates per 1200 patient-months. To analyze these findings in a manner consistent with the other studies reviewed, the specific patient numbers and percentages for the individual cardiovascular events were calculated. For overall mortality, the study's data for sudden death and fatal myocardial infarction were combined: 37 of 208 (17.8%)

Table 1. LIPID/ATHEROSCLEROSIS TRIAL RESULTS IN WOMEN: COHORT NUMBERS AND NUMBER AND PERCENT OF WOMEN EXPERIENCING CLINICAL ENDPOINTS

	Total Cohort		Overall Mortality		ACHD Mortality		Other CV Endpoints	
Study	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention
Scottish Physicians Clofibrate Study[17]	62	62	6 (9.7%)	1 (1.6%)			6 (9.7%)	3 (4.8%)*
Newcastle upon Tyne Clofibrate Trial[18]	45	52	11 (24.4%)	2 (3.8%)			7 (15.6%)	3 (5.8%)*
Minnesota Coronary Survey[19]	2320	2344	95 (4.1%)	111 (4.7%)			47 (2.0%)	62 (2.6%)†
Upjohn Colestipol Study[21]	583	601	21 (3.6%)	20 (3.3%)	9 (1.5%)	10 (1.7%)		
Scandinavian Simvastatin Survival Study (4)[22]	420	407	25 (6.0%)	27 (6.6%)	17 (4.0%)	13 (3.2%)	91 (21.7%)	59 (14.5%)‡
Pravastatin Limitation of Atherosicerosis in the Coronary Arteries (PLAC I) Study[23]	48	44	1 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (8.3%)	0 (0.0%)§
Program on the Surgical Control of the Hyperlipidemias (POSCH) update	32	46	5 (15.6%)	8 (17.4%)	0 (0.0%)	4 (8.7%)	7 (21.9%)	10 (21.7%)‖

ACHD = atherosclerotic coronary heart disease; CV = cardiovascular
* First nonfatal myocardial infarction, definite and probable
† Myocardial infarction, sudden death, and stroke
‡ ACHD death, nonfatal confirmed or probable myocardial infarction, silent myocardial infarction, resuscitated cardiac arrest
§ Myocardial infarction
‖ ACHD mortality or confirmed nonfatal myocardial infarction

in the placebo group men, 23 of 192 (12%) in the clofibrate group men; and 11 of 45 (24.4%) in the placebo group women, 2 of 52 (3.8%) in the clofibrate group women. The authors provided numbers for first nonfatal myocardial infarction: 39 of 208 (18.8%) in the placebo group men, 27 of 192 (14.1%) in the clofibrate group men; and 7 of 45 (15.6%) in the placebo group women, and 3 of 52 (5.8%) in the clofibrate group women. The data for the women are summarized in Table 1.

Minnesota Coronary Survey

The Minnesota Coronary Survey[19,20] used dietary intervention in an institutional setting. The results of this large study, which included more than 9000 patients, were published in 1973[19] in abstract form and subsequently as a manuscript in 1989.[20] Certain patient and event numbers are different in these two presentations. It would seem that there were no specific inclusion criteria for the patients studied. Although the net overall total cholesterol reduction rate was 13.8%, because of the ability of the investigators to regulate the diets of their institutionalized participants, a slight increase in cardiovascular events was found in the total treatment group. One half of the subjects were women, making the Minnesota Coronary Survey the lipid/atherosclerosis intervention trial with the largest number of women participants (4842 listed in 1973 and 4664 listed in 1989). In this female cohort, there was a definite 15.6% increase in overall mortality rate (95/2320, 4.1% controls *vs.* 111/2344, 4.7% diet-treated, using the 1989 data) and a 30.6% increase in the combined endpoint rate of myocardial infarction, sudden death, and stroke (47/2320, 2% controls *vs.* 62/2344, 2.6% diet-treated, using the 1989 data) in the diet-treated intervention group (Table 1).

Upjohn Colestipol Study

The Upjohn Colestipol Study[21] was a randomized trial conducted in 2278 patients with hypercholesterolemia, 1184 of whom were women. The intervention group was treated for up to 3 years with the bile acid binding resin colestipol. This was a mixed primary and secondary intervention trial, with approximately 25% of the patients having sustained a prior myocardial infarction. There were no statistically significant differences in any of 14 baseline variables between the women randomly assigned to the placebo or to the colestipol group. After 1 month, total cholesterol levels declined by 32 mg/dL in the colestipol group and by 1 mg/dL in the placebo group. Total cholesterol reductions in all observation periods averaged 37 mg/dL in the colestipol group and 7 mg/dL in the placebo group. The authors reported the results in the men and in the women separately. The ACHD mortality rate was lower in the colestipol-treated men than in the placebo-treated men ($p \leq 0.02$). The overall mortality rate ($p \leq 0.01$), and the ACHD mortality rate ($p \leq 0.01$) were significantly lower in men with pre-existing ACHD treated with colestipol *versus* men with pre-existing ACHD in the placebo group. For the women, the overall mortality rate was 3.6% (21/583) in the placebo group and 3.3% (20/601) in the colestipol group (p = not significant [NS]), and the ACHD mortality rate was 1.5% (9/583) in the placebo group and 1.7% (10/601) in the colestipol group (p = NS; Table 1). The

authors specifically commented that the mortality rates in the women, most of whom were postmenopausal, were not significantly different between the two treatment groups. Furthermore, the authors stated that these results were comparable to those reported by the Minnesota Coronary Survey[20] in failing to demonstrate an effect of either a cholesterol-lowering diet or a cholesterol-lowering drug on mortality rates in women.

Scandinavian Simvastatin Survival Study

The findings of the Scandinavian Simvastatin Survival Study (4S)[22] are most compelling in questioning the clinical benefits of effective total cholesterol and LDL cholesterol lowering in women, even though the authors do not draw this conclusion themselves. The 4S trial is, to date, the only secondary lipid/atherosclerosis intervention trial to demonstrate a highly statistically significant reduction in both overall mortality ($p = 0.0003$) and in ACHD mortality ($p = 0.00001$) in the total trial population. However, this trial failed to show similar mortality differences in the cohort of women patients. The 4S trial used the hydroxymethyglutaryl-coenzyme A (HMG-CoA) reductase inhibitor simvastatin as the intervention modality. The study was designed to have a 95% power to detect a 30% reduction in overall mortality at a two-sided alpha of 0.05. To achieve this statistical power, the protocol specified the recruitment of 4400 patients to be followed until the occurrence of 440 deaths. The actual number of patients enrolled was 4444, for a median follow-up time of 5.4 years (range, 4.9–6.3 years). In addition to determining the number of deaths *a priori,* the trial design specified a reduction in the total cholesterol level to between 3.0 to 5.2 mmol/L (range, 116–193 mg/dL). Patients were started on 20 mg of simvastatin daily; 37% of the patients were increased to 40 mg of simvastatin daily, and two patients were reduced to 10 mg of simvastatin daily. Over the course of the study, the mean percent changes from baseline for the simvastatin group were −25% for total cholesterol, −35% for LDL cholesterol, +8% for HDL cholesterol, and −10% for triglycerides. The authors did not comment on any differences between the men and the women with respect to the lipid changes.

For the total study population, the overall mortality rate was 11.5% (256/2223) in the placebo group and 8.2% (182/2221) in the simvastatin group, for a relative risk of 0.70 (95% confidence interval [CI], 0.58–0.85). The ACHD mortality rate was 8.5% (189/2223) in the placebo group and 5% (111/2221) in the simvastatin group, for a relative risk of 0.58 (95% CI, 0.46–0.73). In addition, the authors examined a combined endpoint of major coronary events: ACHD death, nonfatal confirmed or probable myocardial infarction, silent myocardial infarction, or resuscitated cardiac arrest. This combined endpoint occurred in 622 of 2223 (28%) patients in the placebo group, and in 431 of 2221 (19%) patients in the simvastatin group, for a relative risk of 0.66 (95% CI, 0.59–0.75).

The overall mortality rate for the women was 6% (25/420) in the placebo group and 6.6% (27/407) in the simvastatin group, for a relative risk of 1.12 (95% CI, 0.65–1.93). The ACHD mortality rate in the women was 4% (17/420) in the placebo group and 3.2% (13/407) in the simvastatin group. For the combined endpoint of major coronary events in the women, there were 91 of 420 (21.7%) in the placebo group and 59 of 407 (14.5%) in the simvastatin group, for a relative risk of 0.65 (95% CI, 0.47–0.91). The data for the women are presented in Table 1. The authors presented the p value for this combined endpoint as 0.01, favoring a beneficial effect in the simvastatin group. They did not provide the p values for overall mortality or for ACHD mortality in the women, or the relative risk and CI for ACHD mortality in the women. By our calculations, they are $p = 0.686$ for overall mortality and $p = 0.512$ for ACHD mortality, with a relative risk of 0.79 (95% CI, 0.39–1.60) for ACHD mortality.

Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I) Study

The most recently reported lipid/atherosclerosis intervention trial to publish data in women was the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I) Study.[23] Performed in 408 patients with mild to moderate elevations in cholesterol levels (LDL cholesterol $\geq$ 130 mg/dL but <190 mg/dL), this secondary intervention trial randomized patients to receive pravastatin or placebo. The PLAC I Study was a 3-year study, and atherosclerosis progression was evaluated by quantitative coronary arteriography, although clinical endpoints also were recorded. Pravastatin decreased total and LDL cholesterol and triglyceride levels by 19%, 28%, and 8%, respectively, and increased the HDL cholesterol level by 7% ($p \leq 0.001$). Progression of atherosclerosis assessed by minimal vessel diameter was reduced by 40% ($p = 0.04$), particularly in lesions with <50% stenosis at baseline. There were 17 fatal and nonfatal myocardial infarctions in the 202 patients in the placebo group, and 8 in the 206 patients in the pravastatin group ($p < 0.05$). There were two ACHD deaths in each group, and overall mortality was five in the placebo group and three in the pravastatin group. For the 92 women (48 placebo group, 44 pravastatin group), there was a statistically significant difference in myocardial infarctions favoring the pravastatin group (4 in the control group, 0 in the pravastatin group; $p = 0.04$; Table 1). There was one noncardiac death in the placebo group women and no deaths in the pravastatin group women.

Program on the Surgical Control of the Hyperlipidemias (POSCH)

The POSCH results in women, originally reported in 1992,[2] have been updated; the overall results are assessed for the total group, for the men, and for the women at three time intervals: on July 19, 1990 (formal trial closure), on September 30, 1992, and on September 30, 1995. Student's t tests were performed between the diet-treated control group and the diet plus partial ileal bypass-treated intervention (surgical) group for the following baseline variables: total cholesterol, LDL cholesterol, HDL cholesterol, very low density lipoprotein cholesterol, fasting blood glucose, age, angina status, systolic blood pressure, diastolic blood pressure, ejection fraction, extent of coronary artery disease, height, weight, Quetelet index (weight in g/height in cm^2), and cigarette smoking status. No statistically significant differences were found between the 32 women in the control group and the 46 women in the surgery group. We also performed Cox regression analysis using the following 13 baseline variables: total cholesterol, LDL cholesterol, HDL cholesterol, very low density lipoprotein cholesterol, fasting blood glucose, systolic blood pressure, diastolic blood pressure, ejection fraction, extent of coronary artery disease, weight, Quetelet index, cigarette smoking status (never, past, present), and menopausal status. Again, no statistically significant differences in the distribution of these baseline variables were found between the control and the surgery group women. Most of the women in POSCH were postmenopausal: 26 (81.3%) of the controls and 38 (82.6%) of the surgery patients.

At 5 years, the average percent decrease in total cholesterol from baseline in the surgery group *versus* the control group was 22.6% in the total POSCH population ($p < 0.0001$), 22.4% in the POSCH men ($p < 0.0001$), and 23.9% in the POSCH women ($p < 0.0001$). The reductions in the LDL cholesterol level after partial ileal bypass were 36.2% in the total POSCH population ($p < 0.0001$), 36.2% in the POSCH men ($p < 0.0001$), and 36.1% in the POSCH women ($p < 0.001$). For HDL cholesterol, the surgery group elevations were statistically significant in the total POSCH population (5.9%, $p < 0.0001$) and in the POSCH men (5.7%, $p < 0.01$), but not in the POSCH women (8.5%, p = NS) because of the small number of female patients (n = 78, 9.3% of the total population of 838 patients).

For the current analysis, we calculated the Mantel-Haenszel statistic for the clinical endpoints of overall mortality, ACHD mortality, and ACHD mortality or confirmed nonfatal myocardial infarction. These data are presented for the time points July 19, 1990; September 30, 1992; and September 30, 1995 (the 9/30/95 numbers may be subject to some changes after final data certification and editing) for all POSCH patients (n = 838), for the POSCH men (n = 760), and for the POSCH women (n = 78) in Table 2. For the two later analysis times (9/30/92 and 9/30/95), the men demonstrate a beneficial effect favoring intervention for ACHD mortality; the trends in the women are slightly in the opposite direction, but do not reach statistical significance. For overall mortality, the incidence rate in the women on September 30, 1995 is 15.6% (5/32) in the control group and 17.4% (8/46) in the surgery group (p = NS). The ACHD mortality rate is 0% (0/32) in the control group and 8.7% (4/46) in the surgery group (p = NS). The ACHD mortality or confirmed nonfatal myocardial infarction rate is 21.9% (7/32) in the control group and 21.7% (10/46) in the surgery group (p = NS; Table 1).

Table 2. POSCH CLINICAL EVENT RESULTS

		Overall (n = 838)			Men (n = 760)			*Women (n = 78)*		
Clinical Event	Analysis Date	C (n = 417)	I (n = 421)	*p Value**	C (n = 385)	I (n = 375)	*p Value**	C (n = 32)	I (n = 46)	*p Value**
Overall mortality	07/19/90	62	49	0.16420	60	44	0.12590	2	5	0.56089
	09/30/92	76	57	0.06450	74	51	0.03997	2	6	0.36363
	09/30/95	100	82	0.10112	95	74	0.09160	5	8	0.79731
ACHD mortality	07/19/90	44	31	0.13340	44	30	0.11236	0	2	0.23412
	09/30/92	52	35	0.04835	52	32	0.02967	0	2	0.23412
	09/30/95	67	48	0.04481	67	44	0.02552	0	4	0.09012
ACHD mortality or definite nonfatal MI	07/19/90	116	76	0.00099	110	70	0.00211	6	6	0.35439
	09/30/92	129	82	0.00019	122	76	0.00054	7	6	0.25064
	09/30/95	155	103	0.00006	148	93	0.00007	7	10	0.71474

ACHD = atherosclerotic coronary heart disease; MI = myocardial infarction; C = control group; I = intervention group.
* p value by Mantel-Haenszel test.

Table 3. LIPID/ATHEROSCLEROSIS TRIAL RESULTS IN MEN: COHORT NUMBERS AND NUMBER AND PERCENT OF MEN EXPERIENCING OVERALL MORTALITY

Study	Total Cohort		Overall Mortality	
	Control	Intervention	Control	Intervention
Scottish Physicians Clofibrate Study[17]	305	288	32 (10.5%)	33 (11.5%)
Newcastle upon Tyne Clofibrate Trial[18]	208	192	37 (17.8%)	23 (12.0%)
Minnesota Coronary Survey[19]	2196	2197	153 (7.0%)	158 (7.2%)
Upjohn Colestipol Study[21]	546	548	27 (4.9%)	17 (3.1%)
Scandinavin Simvastatin Survival Study (4S)[22]	1803	1814	231 (12.8%)	155 (8.5%)
Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I) Study[23]	154	162	4 (2.6%)	3 (1.9%)
Program on the Surgical Control of the Hyperlipidemias (POSCH) update	385	375	95 (24.7%)	74 (19.7%)

META-ANALYSIS

The overall mortality data for men in the seven studies analyzed are presented in Table 3. The meta-analyses for overall mortality for men and for women are presented in Table 4 and illustrated in Figures 1 and 2, using the random effects model of pooling risk differences between control and treatment groups. The risk difference results are shown because the study control rates can be displayed on the same graph. Similar results are obtained using risk ratios. The pooled risk difference of the seven studies is statistically significant for men (−0.0191, 95% CI, −0.0380–−0.0002, p = 0.048) but not statistically significant for women (−0.0099, 95% CI, −0.0327–0.0128, p = 0.37). When using the fixed effects model, the results are highly statistically significant in the men but again, far from statistically significant in the women: −0.0152 for men (95% CI, −0.0249–−0.0054, p = 0.0023) and 0.0015 for women (95% CI, −0.0080–0.0111, p = 0.76).

In the seven studies, there were 11,173 men and 7066 women. Except for the Newcastle upon Tyne study, the overall mortality rate in the controls (*i.e.*, the baseline risk of the study population) is lower in women. The random effects pooled control overall mortality rates of the seven studies is 10.1% (range, 6.5%–15.4%) for men and 7.3% (range, 4.3%–12.1%) for women. The fixed effects pooled control overall mortality rates weighted by only the study size is 10.3% (range, 9.6%–11.2%) for men and 4.7% (range, 4%–5.4%) for women. Thus, the average baseline overall mortality risk for women in these studies is only about one half of the baseline overall mortality risk for men. It can be seen from the figures for both men and women that no clinical benefit from lipid intervention is found at a control overall mortality rate of less than approximately 10%.

The pooled risk difference of the four low-control overall mortality rate studies for men (Scottish + Minnesota + Upjohn + PLAC I = 6396 patients) is similar (−0.0037, 95% CI, −0.0152–0.0079, p = 0.53) to the pooled risk difference (−0.0003, 95% CI, −0.0144–0.0139, p = 0.97) of the five low-control overall mortality rate studies for women (Scottish + 4S + Minnesota +

Table 4. META-ANALYSIS FOR OVERALL MORTALITY FOR MEN AND WOMEN: RISK DIFFERENCE, RISK RATIO, CONTROL RATE

	Men (11,173)	Women (7066)
Random Effects Model pooling of 7 studies		
Risk difference	−0.0191 (−0.0380 to −0.0002) p = 0.048	−0.0099 (−0.0327 to 0.0128) p = 0.39
Risk ratio	0.81 (0.67 to 0.98) p = 0.027	0.89 (0.60 to 1.32) p = 0.56
Control rate	10.1 (6.5 to 15.4)	7.3 (4.3 to 12.1)
Fixed Effects Model pooling of 7 studies		
Risk difference	−0.0152 (−0.0249 to −0.0054) p = 0.0023	0.0015 (−0.008 to 0.0111) p = 0.76
Risk ratio	0.81 (0.72 to 0.91) p = 0.00027	1.01 (0.82 to 1.24) p = 0.96
Control rate	10.3 (9.6 to 11.2)	4.7 (4.0 to 5.4)

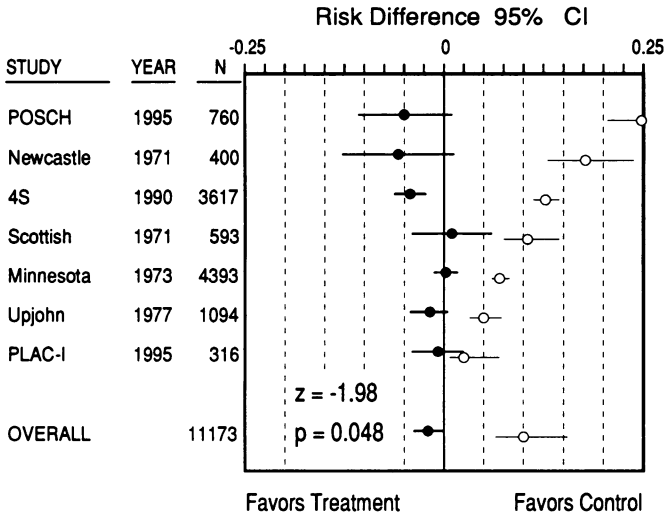

Figure 1. A meta-analysis of the risk differences using overall mortality data for men. Studies are arranged by descending control group event rates. N represents the number of patients in each study. The risk difference of each study and the pooled result are shown as black dots along with their respective 95% confidence intervals. Sharing the graph and the scale (but interpreted as control rate instead of risk differences) are the corresponding control group event rates (open circle) and their 95% confidence intervals. A random effects model was used to pool the risk differences and the control rates.

Upjohn + PLAC I = 6891 patients). No clinical benefit is seen for either men or women in these studies performed in low overall mortality risk populations.

The pooled risk difference of the three high-control overall mortality rate studies for men (POSCH + Newcastle + 4S = 4777 patients) is −0.0444 (95% CI, −0.0627–−0.0261, $p < 0.00001$); the pooled risk difference of the two high-control overall mortality rate studies for women (Newcastle + POSCH = 175 patients) is −0.0996 (95% CI, −0.3185–0.1193, $p = 0.37$). A high degree of statistical significance is found in the studies performed in high overall mortality risk men, but the result seen for women is not significant. However, there are only 175 women in the two high overall mortality risk studies of women *versus* 4777 men in the three high overall mortality risk studies of men.

DISCUSSION

After many years and multiple trials, a critical interpretation of the cumulative clinical trial results supports the conclusion that the lipid/atherosclerosis theory has been proven for men. The lipid/atherosclerosis theory states that elevated total cholesterol levels, elevated LDL cholesterol levels, and low HDL cholesterol levels are associated with increased overall mortality and with increased ACHD mortality and morbidity, and that a substantial lowering of the total cholesterol and LDL cholesterol levels, especially when associated with an increase in the HDL cholesterol level, is associated with a decrease in overall mortality and decreases in ACHD mortality and morbidity. In the Cholesterol Lowering Atherosclerosis Study trial, there was significantly less arteriographic progression of coronary atherosclerosis in the native circulation and in the coronary artery bypass grafts in patients treated with colestipol and nicotinic acid ($p < 0.001$).[7] In the Helsinki Heart Study, the rate for the combined endpoint of three clinical events (fatal myocardial infarction, confirmed nonfatal myocardial infarction, and sudden cardiac death) was significantly lower in patients treated with gemfibrozil ($p = 0.02$).[24] The NHLBI Type II Coronary Intervention Study showed that a reduction in the total cholesterol level by cholestyramine slowed the progression of ACHD assessed by serial coronary arteriograms.[10] The Familial Atherosclerosis Treatment Study, using several dual-drug regimens, reported atherosclerosis regression on sequential coronary arteriograms.[8] The findings of the Arteriosclerosis Specialized Center of Research Study (SCOR), employing a triple-drug regimen, showed a decrease in arteriographic progression and an increase in arteriographic regression in the treatment group.[25] Further confirmation of arteriographic slowing of arteriographic progression of atherosclerosis lesions has been reported by the lifestyle changes and exercise studies.[26] The report from the Mevinolin Atherosclerosis Regression Study (MARS) is again supportive of the benefits of lipid modification.[27] The powerful proof of the lipid/atherosclerosis theory provided by POSCH and by the more recent 4S study have been reviewed in this report.

As a result of these studies, the tacit assumption has been made by the majority of trialists and clinicians that

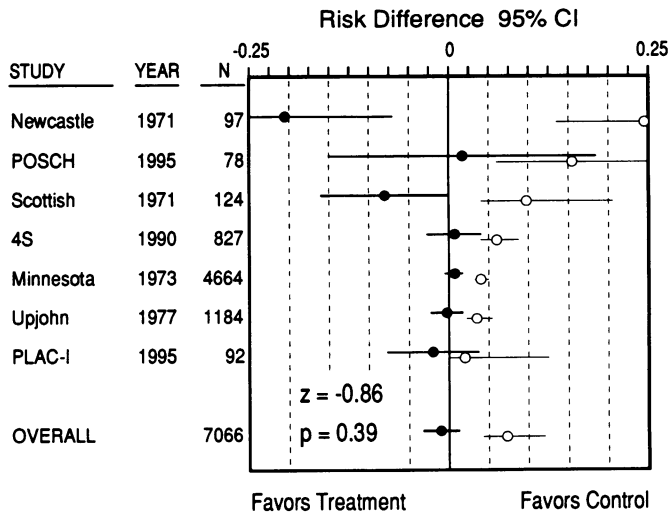

Figure 2. A meta-analysis of the risk differences using overall mortality data for the women (see explanation for Fig. 1).

women are comparable to men with respect to the clinical benefits derived from effective lipid modification. Only the authors of the Upjohn Colestipol Study called attention to a difference in the clinical response to lipid intervention between men and women. The 4S report clearly demonstrated a decrease in overall mortality (relative risk 0.70, p = 0.0003) and in ACHD mortality (relative risk 0.58, p = 0.00001) in the total study population. However, in the women in the 4S report, the relative risk was 1.12 with a p value of 0.686 for overall mortality and 0.79 with a p value of 0.512 for ACHD mortality. In the face of such strong evidence for a positive increase in survival and a decrease in ACHD mortality by effective lipid modification in the total 4S trial population, and even more so in the men in this trial, the striking absence of comparable beneficial effects in the women in the 4S trial is remarkable and should arouse considerable curiosity, despite the fact that only 827 women participated in this trial. The authors of 4S remained silent on this striking lack of clinical benefit in women in their discussion of the 4S trial results.

In POSCH, based on the lipid and arteriographic parallels between the men and the women, we initially projected that effective lipid modification would result in a beneficial clinical effect in women similar to that seen in men. Citing the POSCH and the Kane et al.[25] studies, a recent review of women and ACHD stated, "[t]herefore women with established coronary artery disease should have dyslipidaemia vigorously treated."[28] The National Cholesterol Education Program Second Report recommends lipid management therapy for women.[29] The only recent skeptical report published on the efficacy of lipid modification in women also employed meta-analytic techniques and concluded that there is no evidence for an effect on overall mortality in women in primary intervention trials, but that there is limited evidence to suggest that ACHD mortality may be decreased in women in a secondary intervention setting by hypercholesterolemia management.[30]

For the current analysis, all lipid/atherosclerosis intervention trials—primary or secondary—that included women and that published the data in the women independently of the data in the men or in the total study population have been included. Based on these criteria, only seven studies qualified for review. In four of these studies, the statistical significance of the findings supporting cholesterol intervention in the men and in the total study population would be strengthened if the women were removed from the analysis. Meta-analysis of the findings in the women in these seven studies fails to demonstrate that the women derived any clinical benefit with respect to overall mortality from effective lipid intervention. Stated another way, the null hypothesis that women do not derive clinical benefit from lipid intervention cannot be rejected by the available data.

For comparison, the same meta-analysis was performed on the population of men in the same seven studies for the endpoint of overall mortality. Individually, only in the 4S study was overall mortality significantly reduced in the men. Nevertheless, for the men in these seven studies, there was a definite trend toward a reduction in overall mortality, which was significant.

If we hypothesize that women may not respond clinically to lipid intervention in a favorable manner, how can this hypothesis be criticized? Four broad objections to this hypothesis are discussed. Others can and certainly will be raised.

First and most obvious, there has not yet been a lipid/atherosclerosis intervention trial performed solely in women, or a trial designed to have a high statistical power to demonstrate a favorable outcome with an alpha of 0.05 for women analyzed independently of men. The current Women's Health Care Initiative Study, sponsored by the National Institutes of Health, will recruit approximately 160,000 women and will have a low-fat diet arm in the study.[31] This study may have adequate statistical power to assess the results of lipid intervention in women.

Is it justified to conduct meta-analysis for a subgroup, *i.e.*, for women? In particular, is it justified to select seven trials for meta-analysis on the criteria of having included women and having published analyzable data in women? If all of the data on women in the completed lipid/atherosclerosis intervention trials could be reviewed, the meta-analysis would be strengthened. For this review, however, only seven trials were available. Granting that this particular subgroup meta-analysis can be criticized, meta-analysis is unnecessary to appreciate that women did not demonstrate a beneficial clinical response in four of the seven available studies: the Minnesota Coronary Survey, the Upjohn Colestipol Study, the 4S study, and POSCH.

Were there enough total deaths in the women in the seven trials assessed to allow for an analysis of a difference, or a lack of a difference, between the control and the intervention groups? Women were clearly under-represented in the two studies with high control overall mortality rates for the women. Thus, a pooling of all seven studies without regard for baseline overall mortality risk, as performed in traditional meta-analyses, may obscure the heterogeneity that exists. There simply may not be enough analyzable evidence in high overall mortality risk women to draw any conclusions.

Pooling the data of the seven reviewed studies, the difference in overall mortality rate observed between the pooled control group and the pooled intervention group is 4.8% to 4.5%, or 0.3%, for the women, which is less

than the difference observed for the men (10.3%–8.3%, or 2%). Assuming independent binomial distributions, the probability of obtaining statistical significance, with a two-sided alpha of 0.05, in a study of 7066 women (the combined number of women in the 7 trials), would be >0.90 against an alternative of the magnitude observed in men.

The strongest objection to the hypothesis that women do not respond to lipid intervention comparably to men is raised by the arteriographic studies. Women were included in the NHLBI Type II,[10] SCOR[25] Stanford Coronary Risk Intervention Project (SCRIP),[32] MARS,[27] Lifestyle Heart Trial,[26] and POSCH[1] studies, and apparently the women were no different from the men in demonstrating a reduction in coronary arteriographic lesion progression, and in some studies in demonstrating a regression in lesions, after effective lipid intervention. In POSCH, we based our prior recommendation that women should undergo aggressive management of hyperlipidemia in the general treatment of atherosclerosis on the statistically significant arteriographic evidence of a decrease in coronary artery lesion progression in the treatment group.[2] How can a beneficial arteriographic change be reconciled with no apparent clinical benefit in women? Possibly, there is a difference in thrombotic tendency between men and women, or the degree of intraluminal or intraplaque hemorrhage, thrombus organization, and thrombus incorporation is gender dependent.[33–37] Possibly, the stability of the atherosclerotic plaque; the thickness of the fibrous cap; the tendency for plaque fissuring; and the lipid, collagen, and macrophage content of plaques are different between men and women.[35,38,39] Human panel or computer-assisted arteriographic assessment techniques will not allow differentiation of a stable from an active plaque.

Based on the available lipid/atherosclerosis intervention trial data in women, we question whether women respond clinically to effective lipid intervention. This question can be posed without any detraction from the conclusion that effective lipid intervention is beneficial in the overall management of atherosclerosis in men. The working hypothesis that women may not respond clinically to effective lipid intervention in a favorable manner has several logical implications. Research is needed to explore possible underlying differences in atherogenesis and atherosclerotic plaque evolution and stabilization between men and women. Certainly, a strong recommendation for a lipid/atherosclerosis intervention trial(s) in women can be made. Such trial(s) must be designed to allow for a sufficient number of susceptible women to be treated with a powerful lipid-lowering agent, with follow-up for an adequate period of time, using clinical and more than just arteriographic endpoints. Finally, we currently would not recommend that clinicians abandon lipid intervention in women, especially in women with overt ACHD. However, we would caution that lipid intervention in women should not give rise to therapeutic complacency and that other risk factor interventions in women should be considered concurrently.

Acknowledgment

This paper is dedicated to Thomas C. Chalmers, M.D., who died on December 27, 1995. Dr. Chalmers was Chairman of the POSCH Data Monitoring Committee since its inception. He will long be remembered for his integrity, his intellect, and his total dedication to randomized clinical trials.

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APPENDIX

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Discussion

DR. JAMES C. THOMPSON (Galveston, Texas): Many of you may know that the National Institutes of Health (NIH) and the American College of Surgeons are interested in promulgating and supporting the development of randomized trials. Many of us have worried about teaching young investigators how to go about learning these difficult methods, how to do these trials properly, and how to avoid the menacing pitfalls of statistical error that often invalidate years of work. Fortunately, we have several outstanding surgical practitioners of this arcane art. They are an invaluable resource.

You heard in discussion this morning from Marshall Orloff, who, with continuous NIH support for approximately 30 years, has been studying the best way to treat complications of portal hypertension. In this paper, Henry Buchwald shows another example of his mastery of this technique. He and Tom Chalmers and their colleagues spent years defining the questions to be asked, recruiting proper patients, creating appropriate controls, and devising and enforcing strict criteria for inclusions and exclusions.

Today we learned that the women patients in the Program on the Surgical Control of the Hyperlipidemias (POSCH) study fail to show benefit from lowering lipid levels. To cap that off, they show that with near unanimity, the seven trials that they fused together in meta-analysis have all agreed. Currently, women do die of coronary artery disease and strokes. You have to wonder, have the death rates in these two diseases in women fallen as they have in men for the last 5 to 7 years?

What can you tell us about the mechanisms of the protective effects of estrogens on coronary artery disease? I know you have thought a lot about this. Is this just a statistical problem because the death rates in women are so low to begin with that you may need to study 10,000 women to show an effect? That is what you presume in your recommendation to mount yet another study, the Henry Buchwald Unemployment Act.

Do you have information on pre- and postmenopausal morbidity and mortality as affected by lipid levels? In other words, if you do lower lipid levels in premenopausal women and postmenopausal women, is there a difference? Are there data on the possible mechanistic interactions between estrogen and lipids as they affect coronary artery atherogenesis? That is, we know that the incidence of coronary artery disease increases with menopause because estrogen levels lower the incidence of coronary artery disease. This leads to the question as you try to digest this information, should the Food and Drug Administration approve cholesterol-lowering drugs for men only, because apparently they have scant effect on women?

Let me just say that if you are looking for a consultant for a planned prospective randomized trial, you could hardly find a better person than Henry Buchwald.

DR. JOSEF E. FISCHER (Cincinnati, Ohio): Dr. Thompson, as usual, has anticipated many of the points that I wished to make. I want to thank Dr. Buchwald for giving me this complex manuscript in enough time for somebody as unschooled in statistics as I am to perhaps understand it.

Like many good papers, this began with a clinical observation: lack of improvement in outcome in women in lipid and cholesterol manipulation. In reviewing the data, I thought of three possible explanations for this observed effect in addition to the low mortality among women and the statistical aberration that Dr. Buchwald questioned but seems to discard in the manuscript. They are, in no particular order: 1) plaque evolution stabilization as being different in women as opposed to men; 2) cholesterol and triglycerides are not the critical factor in arteriosclerotic heart disease; and 3) the presence of another variable, which none of these trials have looked at.

With plaque stabilization evolution, it is very interesting that the only two trials that are highly significant are the Clofibrate (Scottish) trial and the Newcastle trial. There is some evidence in the literature that plaque stabilization evolution is different in women and in men. Although the effects for this were attributed to their effect on lipids, I suppose it is possible, knowing a little bit about drugs, that it could have effects on plaque stabilization evolution. I would like to ask Dr. Buchwald what he thinks about that.

Second, ever since the initial draft, which I believe was by Aneel Keys, showing the relationship in Western countries of cholesterol and death from arteriosclerotic heart disease, there have been mutterings about the fact that this is not really so and that the true mechanism is not cholesterol and not triglyceride. In the manuscript, Dr. Buchwald seems to accept the fact that lipids and triglycerides are the mechanism in men but questions this in women. High-density lipoprotein cholesterol and the necessitated increase to bring about the desired effect have other variables, such as exercise. Are we dealing with yet another mechanism? I would like to ask Dr. Buchwald what he thinks about that.

Finally, if you are thinking about another variable, Dr. Thompson already has mentioned estrogen status and menopausal status. In the Program on the Surgical Control of the Hyperlipidemias (POSCH) trial, patients are stratified for menopausal status. The numbers of postmenopausal women, approximately 80%, show that this could not possibly affect the outcome. But I wonder about the other trials? Have they been stratified for estrogen and menopausal status? Because that really seems to be the most likely explanation, at least to me, for the failure to observe the desired effect.

DR. MARSHALL Z. SCHWARTZ (Washington, District of Columbia): As a pediatric surgeon, you might wonder why I am discussing this paper. Well, before I became a pediatric surgeon—in fact, before I received an M.D. degree—I started working as a second-year medical student in the laboratory of a young surgeon/scientist at the University of Minnesota named